

## Title (en)

ANTIGEN BINDING PROTEINS TO PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9)

## Title (de)

ANTIGENBINDENDE PROTEINE GEGEN PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYP 9 (PCSK9)

## Title (fr)

PROTÉINES DE LIAISON À UN ANTIGÈNE POUR LA PROPROTÉINE CONVERTASE SUBTILISINE KEXINE DE TYPE 9 (PCSK9)

## Publication

**EP 2215124 B1 20160224 (EN)**

## Application

**EP 08798550 A 20080822**

## Priority

- US 8613308 P 20080804
- US 95766807 P 20070823
- US 2008074097 W 20080822
- US 1063008 P 20080109
- US 896507 P 20071221

## Abstract (en)

[origin: WO2009026558A1] Antigen binding proteins that interact with Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) are described. Methods of treating hypercholesterolemia and other disorders by administering a pharmaceutically effective amount of an antigen binding protein to PCSK9 are described. Methods of detecting the amount of PCSK9 in a sample using an antigen binding protein to PCSK9 are described.

## IPC 8 full level

**C07K 16/40** (2006.01); **A61K 31/22** (2006.01); **A61K 31/366** (2006.01); **A61K 31/40** (2006.01); **A61K 31/405** (2006.01); **A61K 31/44** (2006.01); **A61K 31/47** (2006.01); **A61K 31/505** (2006.01); **A61K 31/66** (2006.01); **A61K 39/00** (2006.01); **A61K 39/395** (2006.01); **A61K 45/06** (2006.01); **A61P 3/06** (2006.01); **C12N 15/113** (2010.01)

## CPC (source: EA EP IL KR US)

**A61K 31/22** (2013.01 - EA EP IL US); **A61K 31/366** (2013.01 - EA EP IL US); **A61K 31/40** (2013.01 - EA EP IL US); **A61K 31/405** (2013.01 - EA EP IL US); **A61K 31/44** (2013.01 - EA EP IL US); **A61K 31/47** (2013.01 - EA EP IL US); **A61K 31/505** (2013.01 - EA EP IL US); **A61K 31/66** (2013.01 - EA EP IL US); **A61K 39/395** (2013.01 - EA EP IL US); **A61K 39/3955** (2013.01 - EA EP IL US); **A61K 45/06** (2013.01 - EA EP IL US); **A61P 3/00** (2018.01 - EP IL); **A61P 3/06** (2018.01 - EP IL KR); **A61P 7/00** (2018.01 - EP IL); **A61P 9/00** (2018.01 - EP IL); **A61P 9/10** (2018.01 - EP IL); **A61P 25/28** (2018.01 - EP IL); **A61P 43/00** (2018.01 - EP IL); **C07K 16/40** (2013.01 - EA EP IL KR US); **C12N 15/1137** (2013.01 - EA IL US); **A61K 2039/505** (2013.01 - EA EP IL KR US); **A61K 2300/00** (2013.01 - IL); **C07K 2299/00** (2013.01 - EA EP IL US); **C07K 2317/14** (2013.01 - EA IL US); **C07K 2317/24** (2013.01 - KR); **C07K 2317/34** (2013.01 - EA EP IL US); **C07K 2317/76** (2013.01 - EA EP IL US); **C07K 2317/92** (2013.01 - EA EP IL KR US)

## C-Set (source: EP US)

1. **A61K 31/22 + A61K 2300/00**
2. **A61K 31/366 + A61K 2300/00**
3. **A61K 31/40 + A61K 2300/00**
4. **A61K 31/405 + A61K 2300/00**
5. **A61K 31/44 + A61K 2300/00**
6. **A61K 31/47 + A61K 2300/00**
7. **A61K 31/505 + A61K 2300/00**
8. **A61K 31/66 + A61K 2300/00**
9. **A61K 39/395 + A61K 2300/00**
10. **A61K 39/3955 + A61K 2300/00**

## Citation (examination)

- EP 2615114 A2 20130717 - AMGEN INC [US]
- LAGACE THOMAS A ET AL: "Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice", JOURNAL OF CLINICAL INVESTIGATION, AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, US, vol. 116, no. 11, 1 November 2006 (2006-11-01), pages 2995 - 3005, XP002493243, ISSN: 0021-9738, DOI: 10.1172/JCI29383
- HYOCK JOO KWON ET AL: "Molecular basis for LDL receptor recognition by PCSK9", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 105, no. 6, 12 February 2008 (2008-02-12), pages 1820 - 1825, XP007912351, ISSN: 0027-8424, DOI: 10.1073/PNAS.0712064105
- DA-WEI ZHANG ET AL: "Binding of Proprotein Convertase Subtilisin/Kexin Type 9 to Epidermal Growth Factor-like Repeat A of Low Density Lipoprotein Receptor Decreases Receptor Recycling and Increases Degradation", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 282, no. 25, 22 June 2007 (2007-06-22), pages 18602 - 18612, XP007912352, ISSN: 0021-9258, [retrieved on 20070423], DOI: 10.1074/JBC.M702027200
- NI YAN G ET AL: "A proprotein convertase subtilisin-like/kexin type 9 (PCSK9) C-terminal domain antibody antigen-binding fragment inhibits PCSK9 internalization and restores low density lipoprotein uptake", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, INC, BETHESDA, MD, USA, vol. 285, no. 17, 23 April 2010 (2010-04-23), pages 12882 - 12891, XP002619048, ISSN: 1083-351X, [retrieved on 20100219], DOI: 10.1074/JBC.M110.113035
- "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) Final Report", 1 September 2002, pages: 3161 - 3167
- SAURABH SAHA ET AL: "Solution Structure of the LDL Receptor EGF-AB Pair", STRUCTURE, vol. 9, no. 6, 1 June 2001 (2001-06-01), US, pages 451 - 456, XP055229481, ISSN: 0969-2126, DOI: 10.1016/S0969-2126(01)00606-2
- STEVEN MALBY ET AL: "The First Epidermal Growth Factor-like Domain of the Low-Density Lipoprotein Receptor Contains a Noncanonical Calcium Binding Site +", BIOCHEMISTRY, vol. 40, no. 8, 1 February 2001 (2001-02-01), US, pages 2555 - 2563, XP055229482, ISSN: 0006-2960, DOI: 10.1021/bi002322l

## Citation (opposition)

Opponent : Eli Lilly and Company

- US 95766807 P 20070823
- US 896507 P 20071221
- US 1063008 P 20080109

- US 8613308 P 20080804
- US 8613309 P
- WO 2009026558 A1 20090226 - AMGEN INC [US], et al
- WO 2008125623 A2 20081023 - NOVARTIS AG [CH], et al
- US 91165407 P 20070413
- WO 2009100297 A1 20090813 - MERCK & CO INC [US], et al
- US 6394908 P 20080207
- US 6657708 P 20080221
- WO 2008057457 A2 20080515 - MERCK & CO INC [US], et al
- WO 2006081171 A1 20060803 - AMGEN INC [US], et al
- WO 2009100297 A1 20090813 - MERCK & CO INC [US], et al
- REQUEST FOR CORRECTION OF INVENTORSHIP, 11 February 2009 (2009-02-11)
- SEIDAH, N.G. ET AL.: "the secretory proprotein convertase neural apoptosis regulated convertase 1", PNAS, vol. 100, no. 3, 2003, pages 928, XP002495458
- ABIFADEL M. ET AL.: "mutations in PCSK9 cause autosomal dominant hypercholesterolemia", NAT. GENET., vol. 34, no. 2, 2003, pages 154, XP002253513
- BENJANNET, S. ET AL.: "narc PCSK9 and its natural mutants", JBC, vol. 279, no. 47, 2004, pages 48875, XP002495460
- TIMMS K.M. ET AL.: "a mutation in PCSK9 causing autosomal dominant hypercholesterolemia in a Utah pedigree", HUM. GENET., vol. 114, no. 4, 2004, pages 349, XP055264602
- MAXWELL K.N ET AL.: "adenoviral mediated expression of PCSK9 in mice results in a low density lipoprotein receptor knockout phenotype", PNAS, vol. 101, no. 18, 2004, pages 7100, XP002493244
- QIAN Y.-W. ET AL.: "secreted PCSK9 downregulates low density lipoprotein receptor through receptor mediated endocytosis", J. LIPID RES., vol. 48, no. 7, 2007, pages 1488, XP055265230
- COHEN J. ET AL.: "low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations", NAT. GENET., vol. 37, no. 2, 2005, pages 161 - 65, XP008102949
- ZHAO Z. ET AL.: "molecular characterization of loss of function mutations in PCSK9 and identification", AM. J. HUM. GENET., vol. 79, 2006, pages 514 - 23, XP055265231
- LAGACE T.A. ET AL.: "secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice", J. CLIN. INVEST., vol. 116, no. 11, 2006, pages 2995, XP002493243
- FISHER T.S. ET AL.: "effects of PH and low density lipoprotein on PCSK9 dependent LDL receptor regulation", J. BIOL. CHEM., vol. 282, no. 28, 10 May 2007 (2007-05-10), pages 20502, XP055265234
- ZHANG D.-W. ET AL.: "binding of proprotein convertase subtilisin/kexin type 9 to epidermal growth factor like repeat", J. BIOL. CHEM., vol. 282, no. 25, pages 18602, XP007912352
- CUNNINGHAM D. ET AL.: "structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia", NAT. STRUCT. MOL. BIOL., vol. 14, no. 5, 15 April 2007 (2007-04-15), pages 413, XP002507497
- ANALYSIS OF THE FEATURES OF CLAIM 1
- ENLARGED VERSION OF FIG. 1 DEPICTING THE NON-LINEAR EPITOPE COMPRISING AMINO ACIDS, pages 187 - 202, 231-246 , and 368-383
- ENLARGED VERSION OF FIG. 2 DEPICTING THE OVERLAP BETWEEN THE AMINO ACID RESIDUES THAT ARE BOUND BY PREFERRED PCSK9-SPECIFIC ANTIBODIES DISCLOSED IN NOVARTIS (D14
- ENLARGED VERSION OF FIG. 3 DEPICTING THE OVERLAP BETWEEN THE AMINO ACID RESIDUES THAT ARE BOUND BY ANTIBODIES DISCLOSED IN NOVARTIS (D14) AND THE RESIDUES POSITIONED WITHIN 8 ANGSTROMS OF 31H4
- ENLARGED VERSION OF FIG. 4 DEPICTING THE AMINO ACID RESIDUES TAUGHT IN PB TO BE BOUND BY THE EGFA DOMAIN OF THE LDL RECEPTOR
- ENLARGED VERSION OF FIG. 5 DEPICTING THE OVERLAP BETWEEN THE AMINO ACID RESIDUES THAT ARE BOUND BY PREFERRED PCSK9-SPECIFIC ANTIBODIES DISCLOSED IN NOVARTIS (D14
- CALCULATION OF IC50 OF THE ANTIBODIES OF D14 TO PCSK9
- NI, Y.G. ET AL.: "A PCSK9-binding antibody that structurally mimics the EGF(A) domain of LDL-receptor reduces LDL cholesterol in vivo", J. LIPID RES., vol. 52, 2011, pages 78, XP002686538
- ATOMIC COORDINATES AND STRUCTURE FACTORS DEPOSITED WITH THE PROTEIN DATA BANK UNDER THE ACCESSION CODE "2XTJ" AND AMINO ACID SEQUENCES OF THE PROTEINS IN FASTA FORMAT
- DECLARATION OF CHADWICK KING SUBMITTED BY PATENTEE, 27 November 2015 (2015-11-27)
- KWON, H.J. ET AL.: "molecular basis for LDL receptor recognition by PCSK9", PNAS, vol. 105, no. 6, pages 1820, XP007912351
- ANTIBODY ENGINEERING, METHODS AND PROTOCOLS, METHODS IN MOLECULAR BIOLOGY, vol. 248, 2004, Totowa, New Jersey, U.S.
- HOOGENBOOM, H.R.: "designing and optimizing library selection strategies for generating high affinity antibodies", TIBTECH, vol. 15, 1997, pages 62, XP004034115
- YANG W.P. ET AL.: "CDR WALKING MUTAGENESIS FOR THE AFFINITY MATURATION OF A POTENT HUMAN ANTI-HIV-1 ANTIBODY INTO THE PICOMOLAR RANGE", J. MOL. BIOL., vol. 254, 1995, pages 392, XP000199739
- ANTIBODIES, A LABORATORY MANUAL, 1988, New York
- RASHID, S. ET AL.: "Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9", PNAS, vol. 102, no. 15, 2005, pages 5374, XP002478031
- PEREZ DE LA LASTRA ET AL.: "Epitope mapping of 10 monoclonal antibodies against the pig analogue of human membrane cofactor protein (MCP)", IMMUNOLOGY, vol. 96, 1999, pages 663 - 670, XP055217740
- NI, Y.G. ET AL.: "A proprotein convertase subtilisin-like/kexin type 9 (PCSK9) C-terminal domain antibody antigen-binding fragment inhibits PCSK9 internalization and restores low density lipoprotein uptake", J. BIOL. CHEM., vol. 285, no. 17, 23 April 2010 (2010-04-23), pages 12882 - 12891, XP002619048
- DECLARATION OF DR DARREN KAMIKURA AND CV
- DECLARATION OF DR MALGORZATA GONCIARZ AND CV
- ILLUSTRATION OF 31H4 BINDING TO HPCSK9
- Opponent : REGENERON PHARMACEUTICALS, INC.
- WO 2008063382 A2 20080529 - MERCK & CO INC [US], et al
- WO 2008057458 A2 20080515 - MERCK & CO INC [US], et al
- WO 2008133647 A2 20081106 - MERCK & CO INC [US], et al
- WO 2008057457 A2 20080515 - MERCK & CO INC [US], et al
- WO 2008125623 A2 20081023 - NOVARTIS AG [CH], et al
- US 91165407 P 20070413
- WO 2008057459 A2 20080515 - MERCK & CO INC [US], et al
- EP 2615114 A2 20130717 - AMGEN INC [US]
- WO 2009055783 A2 20090430 - SCHERING CORP [US], et al
- US 98292207 P 20071026
- WO 2009100297 A1 20090813 - MERCK & CO INC [US], et al
- US 6394908 P 20080207
- US 6657708 P 20080221

- WO 2008105797 A2 20080904 - BRISTOL MYERS SQUIBB CO [US], et al
- GROZDANOV ET AL.: "Expression and localization of PCSK9 in rat hepatic cells", BIOCHEMISTRY AND CELL BIOLOGY. BIOCHIMIE ET BIOLOGIE CELLULA., vol. 84, no. 1, 1 February 2006 (2006-02-01), pages 80 - 92, XP008095646
- MAXWELL: "Adenoviral-mediated expression of Pcsk9 in mice results in a low-density lipoprotein receptor knockout phenotype", PNAS, vol. 101, 4 May 2004 (2004-05-04), pages 7100 - 7105, XP002493244
- RASHID ET AL.: "Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9", PNAS, pages 5374 - 5379, XP002478031
- SUZANNE BENJANNET, ET AL.: "The Proprotein Convertase (PC) PCSK9 Is Inactivated by Furin and/or PC5/6A FUNCTIONAL CONSEQUENCES OF NATURAL MUTATIONS AND POST-TRANSLATIONAL MODIFICATIONS", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 281, 13 October 2006 (2006-10-13), pages 30561 - 30572, XP002506016
- PÉREZ DE LA LASTRA ET AL.: "Epitope mapping of 10 monoclonal antibodies against the pig analogue of human membrane cofactor protein (MCP)", IMMUNOLOGY, vol. 96, 1999, pages 663 - 670, XP055217740
- NI ET AL.: "A PCSK9-binding antibody that structurally mimics the EGF(A) domain of LDL-receptor reduces LDL cholesterol in vivo", JOURNAL OF LIPID RESEARCH., vol. 52, 2011, pages 78 - 86, XP002686538
- CUNNINGHAM ET AL.: "Structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia", NAT. STRUCT. MOL. BIOL., 1 May 2007 (2007-05-01), pages 413 - 419, XP002507497
- QIAN ET AL.: "Secreted PCSK9 downregulates low density lipoprotein receptor through receptor-mediated endocytosis", JOURNAL OF LIPID RESEARCH, vol. 48, 2007, pages 1488 - 1498, XP055265230
- FISHER ET AL.: "Effects of pH and Low Density Lipoprotein (LDL) on PCSK9-dependent LDL Receptor Regulation", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 282, no. 28, 13 July 2007 (2007-07-13), pages 20502 - 20512, XP055265234
- ZHANG ET AL.: "Binding of Proprotein Convertase Subtilisin/Kexin Type 9 to Epidermal Growth Factor-like Repeat A of Low Density Lipoprotein Receptor Decreases Receptor Recycling and Increases Degradation", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 282, 22 June 2007 (2007-06-22), pages 18602 - 18612, XP007912352
- KWON ET AL.: "Molecular basis for LDL receptor recognition by PCSK9", PNAS, vol. 105, 12 February 2008 (2008-02-12), pages 1820 - 1825, XP007912351
- PAUL J CARTER: "Potent antibody therapeutics by design", NATURE REVIEWS IMMUNOLOGY, vol. 6, pages 343 - 357, XP007901440
- "Phage Display of Peptides and Proteins", 1996, article MCCAFFERTY ET AL.: "6 Construction and Screening of Antibody Display Libraries", pages: 79 - 111, XP055609483
- "Antibody Engineering", 2004, article DAVIS ET AL.: "Production of Human Antibodies from Transgenic Mice", pages: 191 - 200, XP055278294, DOI: 10.1385/1-59259-666-5:191
- H R HOOGENBOOM: "Selecting and screening recombinant antibody libraries", NATURE BIOTECHNOLOGY, vol. 23, no. 9, 1 September 2005 (2005-09-01), pages 1105 - 1116, XP002348401
- COHEN ET AL.: "Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751,87", CLINICAL CANCER RESEARCH, vol. 11, 1 March 2005 (2005-03-01), pages 2063 - 2073, XP002433667
- YANG ET AL.: "Fully human anti-interleukin-8 monoclonal antibodies: potential therapeutics for the treatment of inflammatory disease states", JOURNAL OF LEUKOCYTE BIOLOGY, vol. 66, 1 September 1999 (1999-09-01), pages 201 - 410, XP001014326
- BERGE ET AL.: "Missense Mutations in the PCSK9 Gene Are Associated With Hypocholesterolemia and Possibly Increased Response to Statin Therapy", ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, vol. 26, pages 1094 - 1100, XP055144155

Opponent : SANOFI

- EP 2215124 A1 20100811 - AMGEN INC [US]
- US 95766807 P 20070823
- US 896507 P 20071221
- US 1063008 P 20080109
- US 8613308 P 20080804
- WO 2009026558 A1 20090226 - AMGEN INC [US], et al
- WO 2008125623 A2 20081023 - NOVARTIS AG [CH], et al
- US 91165407 P 20070413
- WO 2009100297 A1 20090813 - MERCK & CO INC [US], et al
- US 6394908 P 20080207
- US 6657708 P 20080221
- WO 2008057457 A2 20080515 - MERCK & CO INC [US], et al
- WO 2006081171 A1 20060803 - AMGEN INC [US], et al
- REQUEST FOR CORRECTION OF INVENTORSHIP, 11 February 2009 (2009-02-11)
- SEIDAH, N.G. ET AL.: "the secretory proprotein convertase neural apoptosis regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation", PNAS, vol. 100, no. 3, 2003, pages 928, XP002495458
- ABIFADEL M. ET AL.: "mutations in PCKSK9 cause autosomal dominant hypercholesterolemia", NAT. GENET., vol. 34, no. 2, 2003, pages 154, XP002253513
- BENJANNET, S. ET AL.: "NARC-1/PCSK9 and its natural mutants", JBC, vol. 279, no. 47, 2004, pages 48875, XP002495460
- TIMMS K.M. ET AL.: "a mutation in PCK9 causing autosomal dominant hypercholesterolemia in a Utah pedigree", HUM. GENET., vol. 114, no. 4, 2004, pages 349, XP055264602
- MAXWELL K.N ET AL.: "adenoviral mediated expression of PCSK9 in mice results in a low density lipoprotein receptor knockout phenotype", PNAS, vol. 101, no. 18, 2004, pages 7100, XP002493244
- QIAN Y.-W. ET AL.: "secreted PCSK9 downregulated low density lipoprotein receptor through receptor mediated endocytosis", J. LIPID RES., vol. 48, no. 7, 2007, pages 1488, XP055265230
- COHEN J. ET AL.: "low LDL cholesterol in individuals of African descent resulting fro frequent nonsense mutations in PCSK9", NAT. GENET., vol. 37, no. 2, 2005, pages 161 - 65, XP008102949
- ZHAO Z. ET AL.: "molecular characterization of loss of function mutations in PCSK9 and identification of a compound heterozygote", AM. J. HUM. GENET., vol. 79, 2006, pages 514 - 23, XP055265231
- LAGACE T.A. ET AL.: "secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in the livers of parabiotic mice", J. CLIN. INVEST., vol. 116, no. 11, 2006, pages 2995, XP002493243
- FISHER T.S. ET AL.: "effects of PH and LDL on PCSK9 dependent LDL receptor regulation", J. BIOL. CHEM., vol. 282, no. 28, 10 May 2007 (2007-05-10), pages 20502, XP055265234
- ZHANG D.-W. ET AL.: "Binding of Proprotein Convertase Subtilisin/Kexin Type 9 to Epidermal Growth Factor-like Repeat A of Low Density Lipoprotein Receptor Decreases Receptor Recycling and Increases Degradation", J. BIOL. CHEM., vol. 282, no. 25, pages 18602, XP007912352
- CUNNINGHAM D. ET AL.: "Structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia", NAT. STRUCT. MOL. BIOL., vol. 14, no. 5, 15 April 2007 (2007-04-15), pages 413, XP002507497
- ANALYSIS OF THE FEATURES OF CLAIM 1
- ENLARGED VERSION OF FIG. 1 DEPICTING THE NON-LINEAR EPITOPE COMPRISING AMINO ACIDS 187- 202 , 231-246 , AND 368-383 OF PCSK9 BOUND BY PREFERRED PCSK9-SPECIFIC ANTIBODIES DISCLOSED IN NOVARTIS (D14
- ENLARGED VERSION OF FIG. 2 DEPICTING THE OVERLAP BETWEEN THE AMINO ACID RESIDUES THAT ARE BOUND BY PREFERRED PCSK9-SPECIFIC ANTIBODIES DISCLOSED IN NOVARTIS (D14
- ENLARGED VERSION OF FIG. 3 DEPICTING THE OVERLAP BETWEEN THE AMINO ACID RESIDUES THAT ARE BOUND BY ANTIBODIES DISCLOSED IN NOVARTIS (D14) AND THE RESIDUES POSITIONED WITHIN 8 ANGSTROMS OF 31H4

- ENLARGED VERSION OF FIG. 4 DEPICTING THE AMINO ACID RESIDUES TAUGHT IN PB TO BE BOUND BY THE EGFA DOMAIN OF THE LDL RECEPTOR
- ENLARGED VERSION OF FIG. 5 DEPICTING THE OVERLAP BETWEEN THE AMINO ACID RESIDUES THAT ARE BOUND BY PREFERRED PCSK9-SPECIFIC ANTIBODIES DISCLOSED IN NOVARTIS (D14
- CALCULATION OF IC50 OF THE ANTIBODIES OF D14 TO PCSK9
- NI, Y.G. ET AL.: "a PCSK9 binding antibody that structurally mimics the EGF domain of LDL receptor reduces LDL cholesterol in vivo", J. LIPID RES., vol. 52, 2011, pages 78, XP002686538
- ATOMIC COORDINATES AND STRUCTURE FACTORS DEPOSITED WITH THE PROTEIN DATA BANK UNDER THE ACCESSION CODE: "2XTJ" AND AMINO ACID SEQUENCES OF THE PROTEINS IN FASTA FORMAT
- DECLARATION OF CHADWICK KING SUBMITTED BY PATENTEE AT THE ORAL PROCEEDING, 27 November 2015 (2015-11-27)
- KWON, H.J. ET AL.: "molecular basis of LDL receptor recognition by PCSK9", PNAS, vol. 105, no. 6, 4 February 2008 (2008-02-04), pages 1820, XP007912351
- "Antibody Engineering, Methods and Protocols", METHODS IN MOLECULAR BIOLOGY, vol. 248, 2004, Totowa, New Jersey, U.S., XP055265232
- HOOGENBOOM, H.R.: "designing and optimizing library selection strategies for generating high affinity antibodies", TIBTECH, vol. 15, 1997, pages 62, XP004034115
- YANG W.P. ET AL.: "CDR walking mutagenesis for the affinity maturation of a potent human anti HIV1 antibody into the picomolar range", J. MOL. BIOL., vol. 254, 1995, pages 392, XP000199739
- ANTIBODIES, A LABORATORY MANUAL, 1988, XP055265233
- RASHID, S. ET AL.: "decreased plasma cholesterol and hypersensitivity to statins in mice lacking PCSK9", PNAS, vol. 102, no. 15, 2005, pages 5374, XP002478031
- PEREZ DE LA LASTRA ET AL.: "epitope mapping of 10 monoclonal antibodies against the pig analogue of human membrane cofactor protein (MCP)", IMMUNOLOGY, vol. 96, 1999, pages 663 - 670, XP055217740
- Opponent : Sanofi-Aventis Deutschland GmbH et al.
- WO 2009026558 A1 20090226 - AMGEN INC [US], et al
- WO 2008125623 A2 20081023 - NOVARTIS AG [CH], et al
- WO 2009100297 A1 20090813 - MERCK & CO INC [US], et al
- WO 2008057457 A2 20080515 - MERCK & CO INC [US], et al
- WO 2006081171 A1 20060803 - AMGEN INC [US], et al
- SEIDAH, N.G. ET AL.: "the secretory proprotein convertase neutral apoptosis-regulated convertase 1 (narc-1): liver regeneration and neuronal differentiation", PNAS, vol. 100, no. 3, 2003, pages 928 - 933, XP002495458
- ABIFADEL M. ET AL.: "mutations in pcsk9 cause autosomal dominant hypercholesterolemia", NAT. GENET., vol. 34, no. 2, 2003, pages 154, XP002253513
- BENJANNET, S. ET AL.: "narc-1/pcsk9 and its natural mutants", JBC, vol. 279, no. 47, 2004, pages 48865 - 48875, XP002495460
- TIMMS K.M. ET AL.: "a mutation in pck9 causing autosomal-dominant hypercholesterolemia in utah pedigree", HUM. GENET., vol. 114, no. 4, 2004, pages 349 - 353, XP055264602
- MAXWELL K.N ET AL.: "adenoviral mediated expression of pck9 in mice results in a low density lipoprotein receptor knockout phenotype", PNAS, vol. 101, no. 18, 2004, pages 7100 - 7105, XP002493244
- QIAN Y.-W. ET AL.: "secreted pck9 downregulates low density lipoprotein receptor through receptor mediated endocytosis", J. LIPID RES., vol. 48, no. 7, 2007, pages 1488 - 1498, XP055265230
- COHEN J. ET AL.: "low ldl cholesterol in individuals of african descent resulting from frequent nonsense mutations in pcsk9", NAT. GENET., vol. 37, no. 2, 2005, pages 161 - 165, XP008102949
- ZHAO Z. ET AL.: "molecular characterization of loss of function mutations in pcsk9 and identification of a compound heterozygote", AM. J. HUM. GENET., vol. 79, 2006, pages 514 - 523, XP055265231
- LAGACE T.A. ET AL.: "Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice", J. CLIN. INVEST., vol. 116, no. 11, 2006, pages 2995 - 3005, XP002493243
- FISHER T.S. ET AL.: "Effects of pH and Low Density Lipoprotein (LDL) on PCSK9-dependent LDL Receptor Regulation", J. BIOL. CHEM., vol. 282, no. 28, 10 May 2007 (2007-05-10), pages 20502 - 20512, XP055265234
- ZHANG D.-W. ET AL.: "Binding of Proprotein Convertase Subtilisin/Kexin Type 9 to Epidermal Growth Factor-like Repeat A of Low Density Lipoprotein Receptor Decreases Receptor Recycling and Increases Degradation", J. BIOL. CHEM., vol. 282, no. 25, 2007, pages 18602 - 18612, XP007912352
- CUNNINGHAM D. ET AL.: "Structural and biophysical studies of PCSK9 and its mutants linked to familial hypercholesterolemia", NAT. STRUCT. MOL. BIOL., vol. 14, no. 5, pages 413 - 419, XP002507497
- NI, Y.G. ET AL.: "A PCSK9-binding antibody that structurally mimics theEGF(A) domain of LDL-receptor reduces LDL cholesterol in vivo 1", J. LIPID RES., vol. 52, 2011, pages 78 - 86, XP002686538
- KWON, H.J. ET AL.: "Molecular basis for LDL receptor recognition by PCSK9", PNAS, vol. 105, no. 6, pages 1820, XP007912351
- DAVIS ET AL.: "Antibody Engineering, Methods and Protocols", METHODS IN MOLECULAR BIOLOGY, vol. 248, 2004, Totowa, New Jersey, U.S., XP055265232
- HOOGENBOOM, H.R., TIBTECH, vol. 15, 1997, pages 62, XP004034115
- YANG W.P. ET AL., J. MOL. BIOL., vol. 254, 1995, pages 392, XP000199739
- HARLOW, E. ET AL., ANTIBODIES, A LABORATORY MANUAL, 1988, New York, XP055288200
- RASHID, S. ET AL.: "Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9", PNAS, vol. 102, no. 15, 2005, pages 5374, XP002478031
- PEREZ DE LA LASTRA ET AL., IMMUNOLOGY, vol. 96, 1999, pages 663 - 670, XP055217740

#### Cited by

US11673946B2; US11697683B2; EP3666797A1; EP2215124B1; WO2009026558A1

#### Designated contracting state (EPC)

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE SI SK TR

#### Designated extension state (EPC)

AL BA MK RS

#### DOCDB simple family (publication)

**WO 2009026558 A1 20090226**; AR 068011 A1 20091028; AU 2008288791 A1 20090226; AU 2008288791 B2 20141030; BR 122018012430 B1 20191008; BR 122018012430 B8 20210727; BR PI0816117 A2 20150310; BR PI0816117 B1 20181218; BR PI0816117 B8 20210525; CA 2696252 A1 20090226; CA 2696252 C 20160614; CL 2008002495 A1 20090904; CN 101932607 A 20101229; CN 101932607 B 20140625; CN 104311665 A 20150128; CN 104311666 A 20150128; CN 104311667 A 20150128; CN 112390889 A 20210223; CN 112409489 A 20210226; CN 112415203 A 20210226; CN 113402611 A 20210917; CO 6230997 A2 20101220; CR 11328 A 20100712; CY 1117940 T1 20170426; CY 2016023 I1 20170426; CY 2016023 I2 20170426; CY 2016029 I1 20170426; CY 2016029 I2 20170426; DE 19207796 T1 20220310; DE 19207796 T9 20230223; DE 202008018562 U1 20151102; DK 2215124 T3 20160530; DK 2215124 T4 20240129; DK 3666797 T3 20230530; EA 032106 B1 20190430; EA 201000356 A1 20100830; EP 2215124 A1 20100811; EP 2215124 B1 20160224; EP 2215124 B2 20230719; EP 2215124 B9 20231227; EP 3202791 A1 20170809; EP 3666797 A1 20200617; EP 3666797 B1 20230517; ES 2573258 T3 20160606; ES 2573258 T5 20240223; ES 2917423 T3 20220708; ES 2946083 T3 20230712;



FI 2215124 T4 20231010; FI 3666797 T3 20230525; FR 16C0025 I1 20160708; FR 16C0025 I2 20180608; HK 1143824 A1 20110114; HR P20160494 T1 20160603; HR P20160494 T4 20231027; HR P20230503 T3 20230915; HU E028162 T2 20161228; HU E062493 T2 20231128; HU S1600029 I1 20160928; HU S1600036 I1 20161028; IL 204013 A 20170731; IL 252616 A0 20170731; IL 252616 B 20200531; IL 273353 A 20200531; IL 273353 B1 20230901; IL 273353 B2 20240101; IL 304868 A 20231001; JO P20080381 B1 20230328; JP 2010536384 A 20101202; JP 2014043446 A 20140313; JP 2015166345 A 20150924; JP 2016182114 A 20161020; JP 2018118974 A 20180802; JP 2020058376 A 20200416; JP 2023071833 A 20230523; JP 5441905 B2 20140312; JP 5705288 B2 20150422; JP 5906333 B2 20160420; JP 6638009 B2 20200129; KR 101494932 B1 20150226; KR 101702194 B1 20170203; KR 20100057070 A 20100528; KR 20140064962 A 20140528; KR 20170012592 A 20170202; KR 20180035947 A 20180406; KR 20200074262 A 20200624; KR 20210028741 A 20210312; KR 20220031734 A 20220311; KR 20230080496 A 20230607; LT 3666797 T 20230810; LT C2215124 I2 20230425; LT PA2016021 I1 20160627; LT PA2016025 I1 20160912; LU 93096 I2 20160801; LU 93180 I2 20161018; MA 31978 B1 20110103; MX 2010001921 A 20100311; MX 2020008898 A 20201012; MY 180102 A 20201122; NL 300818 I2 20160714; NO 2016010 I1 20160603; NO 2016015 I1 20160812; NO 2023012 I1 20230320; NZ 584101 A 20120928; PE 20091006 A1 20090814; PE 20131400 A1 20131216; PE 20140014 A1 20140131; PE 20140220 A1 20140221; PE 20140221 A1 20140221; PE 20140231 A1 20140308; PE 20180173 A1 20180122; PE 20221507 A1 20221004; PH 12013502285 A1 20160808; PH 12013502286 A1 20160222; PL 2215124 T3 20160831; PL 2215124 T5 20231120; PL 3666797 T3 20230828; PT 3666797 T 20230607; RS 54756 B1 20161031; RS 64295 B1 20230731; SG 10201710183T A 20180130; SG 184702 A1 20121030; SI 2215124 T1 20160930; SI 2215124 T2 20231130; SI 3666797 T1 20231030; TN 2010000063 A1 20110926; TW 200916481 A 20090416; TW 201500374 A 20150101; TW 201500375 A 20150101; TW 201500376 A 20150101; TW 201716444 A 20170516; TW 201906871 A 20190216; TW 202330625 A 20230801; TW I441833 B 20140621; TW I633122 B 20180821; TW I675846 B 20191101; TW I675847 B 20191101; TW I675848 B 20191101; TW I799416 B 20230421; UA 127402 C2 20230816; US 2009142352 A1 20090604; US 2009326202 A1 20091231; US 2011027287 A1 20110203; US 2012020975 A1 20120126; US 2012020976 A1 20120126; US 2012027765 A1 20120202; US 2012093818 A1 20120419; US 2012213797 A1 20120823; US 2012251544 A1 20121004; US 2013052201 A1 20130228; US 2013058944 A1 20130307; US 2013079501 A1 20130328; US 2013079502 A1 20130328; US 2013085265 A1 20130404; US 2013245235 A1 20130919; US 2014228545 A1 20140814; US 2014228547 A1 20140814; US 2014228557 A1 20140814; US 2014235830 A1 20140821; US 2014235831 A1 20140821; US 2014357850 A1 20141204; US 2014357851 A1 20141204; US 2014357852 A1 20141204; US 2014357853 A1 20141204; US 2014357854 A1 20141204; US 2015031870 A1 20150129; US 2015087819 A1 20150326; US 8030457 B2 20111004; US 8168762 B2 20120501; US 8563698 B2 20131022; US 8829165 B2 20140909; US 8859741 B2 20141014; US 8871913 B2 20141028; US 8871914 B2 20141028; US 8883983 B2 20141111; US 8889834 B2 20141118; US 8981064 B2 20150317; US 9045547 B2 20150602; US 9056915 B2 20150616; US 9493576 B2 20161115; US 9920134 B2 20180320

DOCDB simple family (application)

**US 2008074097 W 20080822;** AR P080103668 A 20080822; AU 2008288791 A 20080822; BR 122018012430 A 20080822; BR PI0816117 A 20080822; CA 2696252 A 20080822; CL 2008002495 A 20080822; CN 200880113475 A 20080822; CN 201410218672 A 20080822; CN 201410218704 A 20080822; CN 201410219429 A 20080822; CN 202011304952 A 20080822; CN 202011305148 A 20080822; CN 202011305376 A 20080822; CN 202110464822 A 20080822; CO 10033833 A 20100323; CR 11328 A 20100323; CY 161100401 T 20160511; CY 2016023 C 20160630; CY 2016029 C 20160812; DE 19207796 T 20080822; DE 202008018562 U 20080822; DK 08798550 T 20080822; DK 19207796 T 20080822; EA 201000356 A 20080822; EP 08798550 A 20080822; EP 16204336 A 20080822; EP 19207796 A 20080822; ES 08798550 T 20080822; ES 13151375 T 20080822; ES 19207796 T 20080822; FI 08798550 T 20160824; FI 19207796 T 20080822; FR 16C0025 C 20160603; HK 10110488 A 20101110; HR P20160494 T 20080822; HR P20230503 T 20080822; HU E08798550 A 20080822; HU E19207796 A 20080822; HU S1600029 C 20160603; HU S1600036 C 20160819; IL 20401310 A 20100217; IL 25261617 A 20170601; IL 27335320 A 20200317; IL 30486823 A 20230731; JO P20080381 A 20080819; JP 2010522084 A 20080822; JP 2013195240 A 20130920; JP 2015033054 A 20150223; JP 2016053430 A 20160317; JP 2018031718 A 20180226; JP 2019231236 A 20191223; JP 2023030747 A 20230301; KR 20107006252 A 20080822; KR 20147010033 A 20080822; KR 20177002015 A 20080822; KR 20187009055 A 20080822; KR 20207017279 A 20080822; KR 20217006673 A 20080822; KR 20227006200 A 20080822; KR 20237017950 A 20080822; LT 19207796 T 20080822; LT PA2016021 C 20160602; LT PA2016025 C 20160816; LU 93096 C 20160601; LU 93180 C 20160818; MA 32677 A 20100308; MX 2010001921 A 20080822; MX 2020008898 A 20100218; MY PI2010000750 A 20080822; NL 300818 C 20160603; NO 2016010 C 20160603; NO 2016015 C 20160812; NO 2023012 C 20230320; NZ 58410108 A 20080822; PE 2008001426 A 20080822; PE 2013000847 A 20080822; PE 2013000872 A 20080822; PE 2013000883 A 20080822; PE 2013000884 A 20080822; PE 2013000885 A 20080822; PE 2017002386 A 20080822; PE 2022001349 A 20080822; PH 12013502285 A 20131111; PH 12013502286 A 20131111; PL 08798550 T 20080822; PL 19207796 T 20080822; PT 19207796 T 20080822; RS P20160312 A 20080822; RS P20230403 A 20080822; SG 10201710183T A 20080822; SG 2012062899 A 20080822; SI 200831608 T 20080822; SI 200832209 T 20080822; TN 2010000063 A 20100205; TW 103110947 A 20080822; TW 103110948 A 20080822; TW 103110949 A 20080822; TW 105124816 A 20080822; TW 107117443 A 20080822; TW 111138485 A 20080822; TW 97132236 A 20080822; UA A201401217 A 20080822; US 19709308 A 20080822; US 201113174423 A 20110630; US 201113251909 A 20111003; US 201113251955 A 20111003; US 201113252016 A 20111003; US 201213422887 A 20120316; US 201213422904 A 20120316; US 201213463751 A 20120503; US 201213494912 A 20120612; US 201213655984 A 20121019; US 201213656392 A 20121019; US 201213682698 A 20121120; US 201313860016 A 20130410; US 201414260975 A 20140424; US 201414260985 A 20140424; US 201414261063 A 20140424; US 201414261065 A 20140424; US 201414261087 A 20140424; US 201414459743 A 20140814; US 201414459768 A 20140814; US 201414459777 A 20140814; US 201414459787 A 20140814; US 201414459844 A 20140814; US 201414487932 A 20140916; US 201414562546 A 20141205; US 47417609 A 20090528; US 90308410 A 20101012